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Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, MD 20857
DOCKET NUMBER: 97D-0483

Re: Guidance for Industry: Food-Effect Bioavailability and Bioequivalence Studies,
DRAFT GUIDANCE


Dear Sir/Madam:

Upon review of the draft guidance titled "Food Effect Bioavailability and Bioequivalence Studies", we wish to discuss the practical issues around the recommended time of drug administration in relation to the time of test meal consumption. The relevant section from the draft guidance is excerpted below:

Fed treatments: Following an overnight fast of at least 10 hours, subjects should be served the test meal and ingest this meal within 30 minutes. The drug product should be administered with 180 mL (6 fl oz) of water immediately (within 5 minutes) after completion of the meal. No food should be allowed for at least 4 hours post-dose. Water can be allowed *ad libitum* after 2 hours. Subjects should be served scheduled standardized meals throughout the remaining study period.

Because of the inherent variability in the time required to complete a meal, the dosing times would be variable, and a preset dosing schedule could not be used, when the subjects are to be dosed "immediately (within 5 minutes) after completion of the meal". According to this scheme, subjects will be dosed in the order that they complete their meal. Subject dosing order would have to be sorted on the fly, within 5 minutes of completion of the breakfast by any individual subject. A hypothetical example is presented below:

Subject #	Time meal	Time meal	Dosing time
1	0700	0710	0715
2	0702	0728	0733
3	0704	0730	0735
4	0706	0715	0720
5	0708	0738	0743
6	0710	0720	0725
7	0712	0731	0736
8	0714	0730	0735
9	0716	0740	0745
10	0718	0735	0740

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As is evident in the following presentation, the unpredictable order of subject dosing would be dictated by the variability in meal consumption time, with the possibility that the dosing time for two or more subjects may coincide:

Dose time	Subject #
0715	1
0720	4
0725	3
0733	2
0736	3 & 8
0740	7
0743	10
0745	5

Since the sampling of blood/plasma is relative to dosing time, the adherence to a dosing schedule from one period to the next could not be maintained. The sampling schedules would also be variable and the ability to preset sampling schedules would be lost. For example, subject #4, who is the second subject to be dosed, would belong to another different order the next time he is to be dosed. In this example only 10 subjects are considered. To meet the statistical criteria of the draft guidance a food effect study may include from about 24 subjects to 40 or more subjects.

It is evident that if the draft guidance recommendation regarding timing is to be followed, the time of dosing and blood sample collection would not be in order of subject number. The interval between subject dosing would be variable. It would not be possible to collect blood samples from consecutive subjects at preset intervals, such as 2 minutes. The unpredictable schedule would undermine one's ability to plan execution of a project.

It is also evident that many standard forms used in the conduct of a study could not be prepared and proofed in advance, if the draft guidance proposed scheme is to be followed. These and other required changes may result in the loss of good control of sample collection times and recordkeeping. Since the accuracy of sample collection times is an essential element of pharmacokinetic studies, the need for stringent compliance with the suggested dosing time should be compared to the potential for a significant increase in errors during the conduct of a study.

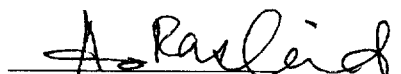
To reduce the potential for errors and to improve the ability to conduct studies efficiently and effectively, we request that the draft guidance stipulations regarding time of dosing relative to meal completion time should be reconsidered. We suggest the following text:

The meal should be served 35 minutes before dosing and subjects should complete the meal within 30 minutes.



Such wording would allow preplanned activities to be executed in a controlled manner. The effect of food on the bioavailability of the product would be adequately tested. All samples could be obtained in a planned manner at accurate times after dosing. The suggested revision would also allow the predose samples to be collected after the meal and before dosing, in an orderly manner.

Sincerely,



Abdur Rashid, Ph.D.

Director, Biopharmaceutics

PharmaKinetics Laboratories, Inc.

April 5, 1999

Cc: Ameeta Parekh, Ph.D.
CDER, FDA

James K. Leslie
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